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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 27716 | 7590 | 10/12/2005 | EXAMINER | |
| CV THERAPEUTICS, INC. 3172 PORTER DRIVE PALO ALTO, CA 94304 | | | BERNHARDT, EMILY B | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1624 | |
| DATE MAILED: 10/12/2005 | | | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/729,499

Applicant(s)

ELZEIN ET AL.

Examiner

Emily Bernhardt

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 8-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 12, 18-21 is/are rejected.
- 7) ☒ Claim(s) 13-17 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>4/19/04</u> . | 6) <input type="checkbox"/> Other: ____. |

PD

Restriction to one of the following inventions is required under 35 U.S.C.

121:

- I. Claims 1-21, drawn to compounds, compositions and uses where $m=1$ and R3-R8 do not form a ring, classified in class 544, subclasses various as determined by R1/R2 among other variables.
- II. Claims 1,2,18-21, drawn to compounds, compositions and uses where $m=1$ and a pair of R3-R8 form a bridged ring, classified in classes such as 540, 544,546 or 548, subclasses various based on the resulting ring system as well as R1/R2.
- III. Claims 1-7,12,18-21, drawn to compounds, compositions and uses where $m=2$ and R3-R8 do not form a ring, classified in class 540, subclass 575; class 514 subclass 218.
- IV. Claims 1,2, 18-21, drawn to compounds, compositions and uses where $m=2$ and a pair of R3-R8 form a bridged ring, classified in classes such as 540,544,546 or 548, subclasses various based on the resulting ring system as well as R1/R2.

Whichever group is elected applicants must further elect a single species and based on species elected further restriction at R1/R2 will be made.

The inventions are distinct, each from the other because of the following reasons:
Groups I-IV are drawn to varying cores which results in compounds of considerable dissimilarity that are not art-recognized equivalents and are variously classified. Each can support a patent as the compounds of each group are capable of being utilized alone not in combination with with other members listed in the Markush group. Within the groups there is more than one invention in view of the varying choices of substituents at either end. Differing issues of patentability may be raised based on the very least the proviso recited at the end of claim 1 for R1 which appears to be necessitated by prior art.

During a telephone conversation with Ms. Hartrum on 9/26/05 a provisional election was made with right of traverse to prosecute the invention of I and in particular species covering benzothiazolyl, claims 1-7,12,18-21. Affirmation of this election must be made by applicant in replying to this Office action. Claims 8-11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Based on species elected further restriction will be made at R1 and R2 requiring both to be heteroaryl as applicants requested this subject matter be particularly examined.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The abstract of the disclosure is objected to because it does not convey the structural makeup of applicants' invention. Correction is required. See MPEP § 608.01(b).

Claims 1-7,12, 18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specification is not adequately enabled for the scope of piperazines claimed at R1/R2 and for substituted derivatives which from a reading of the specification can have as many as 4 hetero atoms in any array, both monocyclic and polycyclic, and which can be further substituted with many more diverse functional groups including hetero rings. Compounds made and tested (which have been searched)

do not represent such a scope as the rings for R1 made are thiazole, quinoline and carbazole and for R2 is primarily benzothiazole along with benzooxazole.

Substitution thereon is consistently the same type of groups, namely alkyl, phenyl and chlorophenyl. There is no reasonable basis for assuming that the myriad of compounds embraced by the broader generic claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey* 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in *In re Wands* cited in MPEP 2164.01(a), August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the millions as pointed out above;

2) Level of unpredictability in the art- the invention is pharmaceutical in nature as it involves inhibition of a biological process. It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved” and physiological activity is generally considered to be unpredictable. See *In re Fisher* 166 USPQ 18. No data is reported in the

specification but only a statement that compounds have been found active as fatty acid oxidation inhibitors;

3) Direction or guidance- as stated above the compounds made are not representative of the instant scope but are closer to each other than to remaining scope ;

4) State of the prior art- The compounds are piperazine derivatives with certain linking groups connecting the ring nitrogen atoms and to which heteroaryl rings are attached. While similar compounds are known in the art having a similar backbone and for the same activity, they do not evidence the many structural permutations permitted in the instant scope;

5) Working examples- As no test data has been presented there is thus no clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the diseases recited in 19 and 20, does not reasonably provide enablement for any and all cardiovascular diseases claimed in 18. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Cardiovascular disorders embraces a vast array of problems, some of which are contradictory to others. This covers various forms of endocarditis, including Verrucous, Atypical verrucous (Libman-Sacks) Non-bacterial thrombotic - NBTE (marantic), bacterial, viral, and rickettsial endocarditis. It covers different forms of atresia, including tricuspid atresia without TGV, pulmonic valvular atresia and aortic atresia. It includes assorted cardiomyopathies, including restrictive cardiomyopathy, peripartum cardiomyopathy, hypertrophic cardiomyopathy, and congenital cardiomyopathy. It embraces various forms of aortic Stenosis, including valvular aortic Stenosis, idiopathic hypertrophic sub-aortic stenosis (IHSS), subvalvular aortic stenosis, and supravalvular aortic stenosis. There are all kinds of miscellaneous syndromes, including subclavian steal syndrome, Eisenmenger syndrome, mitral valve prolapse (Barlow) syndrome, Aortic arch syndrome, scimitar syndrome, hypoplastic left heart syndrome, Lutembacher syndrome, and superior vena cava syndrome. It covers various forms of hypertension, including primary (idiopathic) pulmonary hypertension, neonatal pulmonary venous hypertension and pulmonary hypertension. It includes aortic aneurysms, including both thoracic and abdominal, as well as mycotic aneurysm. It covers various types

of arrhythmias and atrial fibrillation. It covers elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, and hyperlipoproteinaemias. It covers different forms of ischaemic heart disease including congestive heart failure and myocardial infarction. It covers a vast array of structural defects such as atrial septal defect (ASD), aortopulmonary window, egg-on-its-side heart, gooseneck deformity, endocardial cushion defect, arc of Buehler, arc of Riordan, truncus arteriosus, Ebstein's Malformation, azygos continuation of interrupted IVC, Atrioventricular Canal, ventricular septal defect (VSD), abdominal aortic coarctation, aortic pseudo-coarctation, complete endocardial cushion defect, Hypoplastic Left Heart, patent ductus arteriosus (PDA), congenital absence of pulmonary valve, aortic coarctation partial endocardial cushion defect, Single Ventricle, box-like heart, pulmonary sling, Left Ventricle to Right Atrial Shunt, total anomalous pulmonary venous return (TAPVR), partial anomalous pulmonary venous return (PAPVR), and transposition of the great vessels. It covers certain peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis and assorted cerebral vascular diseases including migraine. There is hypotension, which can arise from all sorts of other problems. There are a number of different forms of vasculitis, including Churg-Strauss vasculitis, consecutive vasculitis, granulomatous vasculitis of central

nervous system, hypersensitivity vasculitis, (called also allergic or leukocytoclastic vasculitis or leukocytoclastic angiitis which arises from hypersensitivity to an antigenic stimulus), hypocomplementemic vasculitis, isolated vasculitis of central nervous system, nodular vasculitis, overlap vasculitis (polyangiitis overlap syndrome), pulmonary vasculitis including Wegener's granulomatosis, rheumatoid vasculitis, segmented hyalinizing vasculitis (livedo vasculitis), Polyarteritis nodosa, and urticarial vasculitis. There are also specific forms of arteritis, including coronary arteritis, equine viral arteritis, giant cell arteritis (cranial, granulomatous, or temporal arteritis or Horton's disease), infantile arteritis, infectious arteritis, arteritis obliterans (endarteritis obliterans), rheumatic arteritis, syphilitic arteritis, Takayasu's arteritis (aortic arch, or brachiocephalic arteritis or Martorell's syndrome or pulseless disease), tuberculous arteritis, endarteritis obliterans, arteritis umbilicalis, and verminous mesenteric arteritis. There are different forms of Vascular dementia, including multi-infarct dementia (MID), Binswanger's Disease and Arteriosclerotic Dementia. There is a huge collection of other cardiovascular problems, including thymoma (invasive and non-invasive), admixture lesion, left ventricular hypertrophy, tortuous aorta, aortic laceration pulmonary artery sarcoma, aortic regurgitation, pneumomediastinum (Spontaneous and traumatic), middle mediastinal mass,

posterior mediastinal mass, Uhl disease, right ventricular hypertrophy, cardiac rhabdomyoma, acute aortic dissection, pericardial cyst, carotid artery bruit, pulmonary embolism, venous angioma, varicose veins and spider veins, congenital heart disease, pericardial effusion, tetralogy of Fallot, coronary artery calcification, endocardial fibroelastosis, fibromuscular dysplasia (FMD), thromboangiitis obliterans (Buerger disease), left or right ventricular volume overload, situs inversus, neonatal heart failure, myocarditis, arteriosclerosis, atherosclerosis, stroke and many others.


References cited by applicants (McCormick or Zacharowski) directed to fatty acid oxidation inhibitors such as ranolazine do not make such assertions nor is there evidence of any such compounds known to treat such a range of diseases.

Claims 13-17 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants' IDS filed 6/25/04 cannot be considered at this time since the references are not seen in the electronic file.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.


Emily Bernhardt
Primary Examiner
Art Unit 1624